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Regenerative Endodontics: Biological Basis, Clinical Protocols, and Outcomes

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ABSTRACT

Regenerative endodontic procedures have emerged as a paradigm-shifting approach in the management of immature permanent teeth with pulp necrosis, offering a biologically driven alternative to traditional apexification techniques. Unlike conventional approaches that merely create an apical barrier, regenerative strategies aim to restore functional pulp-like tissue within the root canal system, thereby promoting continued root development, dentinal wall thickening, and apical closure. The biological foundation of regenerative endodontics rests upon three fundamental pillars of tissue engineering: stem cells, bioactive scaffolds, and growth factors. Stem cells of the apical papilla, surviving within the periapical region even after pulp necrosis, represent a critical cellular resource capable of differentiating into odontoblast-like cells and contributing to the formation of mineralized tissue. Clinical protocols have evolved considerably since the earliest case reports, with contemporary guidelines emphasizing thorough canal disinfection using minimally cytotoxic irrigants and intracanal medicaments, followed by the intentional induction of a blood clot scaffold through periapical instrumentation. Bioactive materials such as mineral trioxide aggregate and bioceramic cements serve as coronal barriers, providing a biocompatible seal that supports tissue regeneration. Reported clinical outcomes include resolution of periapical pathology, continued root lengthening, increased root wall thickness, and apical closure, although the histological nature of the regenerated tissue remains a subject of ongoing investigation. This narrative review comprehensively examines the biological underpinnings, contemporary clinical protocols, and documented outcomes of regenerative endodontic procedures, while critically evaluating current controversies, limitations, and future directions in this rapidly evolving field.

Introduction

The management of immature permanent teeth with pulp necrosis and apical periodontitis represents one of the most challenging clinical scenarios in endodontics. These teeth, typically affected by traumatic injuries or developmental anomalies such as dens evaginatus, present with incomplete root formation characterized by thin fragile dentinal

walls, divergent open apices, and an absence of the natural apical constriction necessary for conventional root canal obturation ^[1]. Historically, the treatment of such teeth relied upon apexification procedures using long-term calcium hydroxide therapy to induce apical hard tissue barrier formation, or more recently, the placement of an artificial apical plug using mineral trioxide aggregate ^[2]. While both approaches can effectively manage periapical infection and

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create conditions permitting root canal obturation, neither promotes further root maturation. Consequently, the treated tooth remains structurally compromised, with thin walls that are highly susceptible to cervical root fracture, a complication associated with significant rates of eventual tooth loss [3].

Regenerative endodontic procedures emerged from the convergence of advances in stem cell biology, tissue engineering principles, and clinical observations that disinfected necrotic immature teeth could, under certain conditions, demonstrate continued root development [4]. The pioneering case reports published in the early 2000s demonstrated that following canal disinfection and the induction of bleeding from the periapical tissues into the canal space, immature teeth could exhibit radiographic evidence of root lengthening, wall thickening, and apical closure [5]. These observations catalyzed intense research interest and led to the formal recognition of regenerative endodontic procedures by professional organizations, including the American Association of Endodontists, which published clinical considerations and protocols to guide practitioners [6].

Despite remarkable clinical progress, significant controversies persist regarding the true nature of the tissue formed within regenerated canals, the optimal disinfection protocols, the ideal scaffold material, and the predictability of functional outcomes. The objective of this narrative review is to critically examine the biological basis of regenerative endodontics, evaluate contemporary clinical protocols and their rationale, synthesize the available evidence on clinical and histological outcomes, and identify current knowledge gaps and future research directions.

Biological Basis of Regenerative Endodontics

The Tissue Engineering Triad

Regenerative endodontics is fundamentally grounded in the principles of tissue engineering, which requires the coordinated interaction of three essential components: stem cells capable of differentiating into the desired tissue types, a scaffold providing structural support and spatial guidance for cellular organization, and signaling molecules directing cellular behavior including proliferation, migration, and differentiation [7]. Understanding how each element contributes to regenerative outcomes is essential for optimizing clinical protocols and improving treatment predictability.

Stem Cell Populations

The discovery of dental stem cell populations has been instrumental in establishing the biological plausibility

of pulp regeneration. Several distinct populations of mesenchymal stem cells have been identified within dental and periapical tissues. Stem cells of the apical papilla, first characterized and described in landmark studies, reside in the apical papilla tissue loosely attached to the developing root apex [8]. These cells exhibit remarkable proliferative capacity, express mesenchymal stem cell markers including STRO-1 and CD146, and demonstrate the ability to differentiate into odontoblast-like cells capable of producing dentin-like mineralized tissue both in vitro and in vivo [9]. Crucially, research has demonstrated that stem cells of the apical papilla can survive pulp necrosis and periapical infection, likely owing to their collateral blood supply from the apical and periapical vasculature, which is independent of the pulp circulation [10]. This survival capacity provides the fundamental cellular resource for regenerative processes following clinical intervention.

Additional stem cell populations that may contribute to regeneration include dental pulp stem cells from any surviving pulp tissue remnants, periodontal ligament stem cells, and bone marrow mesenchymal stem cells from the surrounding alveolar bone [11]. The relative contribution of each population to the regenerative outcome remains an active area of investigation, though evidence increasingly suggests that stem cells of the apical papilla play the predominant role in immature teeth.

Scaffold Systems

The scaffold serves as a three-dimensional framework that supports cell attachment, proliferation, and spatial organization during tissue formation. In clinical regenerative endodontic procedures, the evoked blood clot has served as the primary scaffold since the earliest protocols were developed [12]. The blood clot provides a fibrin network that entraps platelets, growth factors, and circulating stem cells, creating a provisional matrix conducive to cellular ingrowth and tissue formation. However, the blood clot possesses inherent limitations including unpredictable formation, inconsistent composition, and rapid degradation, which may contribute to the variability in clinical outcomes observed across studies [13].

Alternative scaffold systems have been investigated to address these limitations. Platelet-rich plasma and platelet-rich fibrin represent autologous concentrates that provide both a structured fibrin scaffold and supraphysiological concentrations of growth factors derived from platelet degranulation [14]. Research has demonstrated that platelet-rich fibrin, in particular, offers a more stable and slowly degrading scaffold compared to the blood clot alone, with sustained release of growth factors over extended periods. Synthetic and natural biomaterial scaffolds, including injectable hydrogels, collagen matrices, and self-assembling peptide nanofibers, have shown promising results in

preclinical studies but have not yet achieved widespread clinical adoption ^[15].

Growth Factors and Signaling Molecules

Growth factors orchestrate the cellular processes necessary for tissue regeneration, including chemotaxis, angiogenesis, cellular proliferation, and differentiation. Within the context of regenerative endodontics, dentin itself serves as a critical reservoir of bioactive molecules. Research has revealed that the dentin matrix contains sequestered growth factors including transforming growth factor-beta, bone morphogenetic proteins, vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor, which were incorporated during dentinogenesis and can be released by conditioning agents, EDTA irrigation, or the mild acidic environment associated with tissue remodeling ^[16]. Studies have confirmed that EDTA conditioning of dentin surfaces significantly enhances the release of these growth factors and promotes the attachment, migration, and differentiation of dental stem cells ^[17]. This understanding has directly influenced clinical protocol modifications, with EDTA irrigation now recommended as a penultimate step before blood clot induction.

Clinical Protocols

Patient Selection and Diagnosis

The ideal candidate for regenerative endodontic procedures is a young patient with an immature permanent tooth demonstrating pulp necrosis with or without periapical pathology. The American Association of Endodontists clinical considerations specify that the tooth should have an open apex with a minimum apical diameter sufficient to permit vascular ingrowth and cellular migration into the canal space ^[6]. Teeth with fully formed apices may also be considered, although the evidence supporting regeneration in mature teeth remains limited and largely experimental ^[18]. Accurate diagnosis requires careful clinical and radiographic evaluation, including vitality testing, periapical radiography, and preferably cone-beam computed tomography for detailed assessment of root development stage and periapical status.

Disinfection Protocols

Effective canal disinfection is recognized as the single most critical determinant of regenerative success, as residual bacteria compromise stem cell survival and tissue formation. However, the disinfection strategy must balance antimicrobial efficacy against cytotoxicity to vital stem cells in the periapical region ^[19]. Contemporary protocols emphasize

gentle, copious irrigation with sodium hypochlorite at reduced concentrations, typically 1.5% rather than the higher concentrations used in conventional endodontics, to minimize cytotoxic effects on stem cells of the apical papilla while maintaining adequate antimicrobial activity ^[20]. Studies have demonstrated that higher concentrations of sodium hypochlorite significantly reduce stem cell survival and differentiation capacity, potentially compromising regenerative potential.

The triple antibiotic paste, comprising ciprofloxacin, metronidazole, and minocycline, was introduced as an intracanal medicament based on research demonstrating its effectiveness against endodontic polymicrobial infections ^[21]. However, concerns have emerged regarding minocycline-induced tooth discoloration, cytotoxicity at high concentrations, and potential development of bacterial resistance. Modifications to the original formulation have included substitution of minocycline with clindamycin or cefaclor to avoid discoloration, and limitation of paste concentration to 1 mg/mL or lower to reduce cytotoxic effects on stem cells ^[22]. Calcium hydroxide has gained favor as an alternative intracanal medicament, offering effective antimicrobial activity, biocompatibility with stem cells at clinical concentrations, and promotion of dentin-derived growth factor release through its alkaline pH ^[23].

Scaffold Placement and Coronal Seal

Following adequate disinfection, typically over a two-to-four-week interappointment period, the medicament is removed, the canal is irrigated with EDTA to release dentin matrix-derived growth factors, and bleeding is induced from the periapical tissues by instrumenting slightly beyond the apex with a sterile endodontic file ^[6]. The blood clot is allowed to form to a level approximately 3 mm below the cemento-enamel junction. A biocompatible material, most commonly mineral trioxide aggregate or a bioceramic cement such as Biodentine, is placed over the blood clot as a coronal barrier, followed by a permanent coronal restoration to ensure an effective seal against bacterial contamination ^[24]. The integrity of the coronal seal has been identified as a crucial factor in long-term success, as microleakage represents a primary cause of regenerative failure.

Clinical and Histological Outcomes

Clinical and Radiographic Outcomes

A substantial body of evidence now supports the clinical effectiveness of regenerative endodontic procedures for achieving the primary treatment goals defined by professional organizations: elimination of clinical symptoms, resolution of periapical pathology, and ideally, continued root

development [25]. Systematic reviews and meta-analyses have reported periapical healing rates ranging from 91% to 97%, comparable to or exceeding those achieved with apexification techniques [26]. Resolution of signs and symptoms of infection is consistently reported in the vast majority of cases across published studies.

The secondary goals of increased root length and root wall thickness are achieved with greater variability. Radiographic evidence of continued root lengthening has been reported in approximately 60% to 75% of cases, while increases in root wall thickness are observed in approximately 55% to 80% [27]. Apical closure, whether partial or complete, is documented in a high proportion of treated teeth. However, standardized quantitative methods for measuring these changes remain inconsistent across studies, and the clinical significance of incremental changes in root dimensions requires further investigation. Notably, comparative studies have demonstrated that regenerative procedures achieve significantly greater increases in root length and thickness compared to mineral trioxide aggregate apexification, supporting their biological superiority for promoting continued root maturation [28].

Histological Findings

Perhaps the most contentious aspect of regenerative endodontics pertains to the histological nature of the tissue that forms within the canal space. The original aspiration of true pulp-dentin complex regeneration has been tempered by histological findings from both animal studies and the limited number of human teeth available for histological examination. The majority of histological analyses have revealed the formation of cementum-like tissue, bone-like tissue, and periodontal ligament-like connective tissue within the canal lumen, rather than true pulp tissue with organized odontoblasts and tubular dentin [29]. This finding has led to a reconceptualization of the process as one of repair rather than true regeneration in most cases.

Research examining human teeth extracted after regenerative procedures has confirmed the predominance of periodontal-type tissue ingrowth, likely originating from periodontal ligament cells and cementoblasts migrating into the canal space through the open apex [30]. While this tissue provides functional benefits including root wall reinforcement through cementum deposition and potential restoration of some proprioceptive function, it differs fundamentally from the original pulp-dentin complex. Nevertheless, isolated case reports have documented areas of newly formed dentin-like tissue with associated odontoblast-like cells, suggesting that true dentin regeneration may occur under optimal conditions, possibly when stem cells of the apical papilla are successfully recruited and appropriately stimulated [31].

Pulp Sensibility and Vitality

The restoration of pulp sensibility following regenerative procedures has been reported in approximately 40% to 80% of cases, depending on the assessment method and follow-up duration [32]. Positive responses to electric pulp testing and cold testing have been documented, although the interpretation of these findings requires caution. Sensibility testing reflects the presence of functional neural elements within the canal, which may develop within the regenerated tissue regardless of its specific histological composition. Laser Doppler flowmetry studies have confirmed vascular ingrowth in regenerated teeth, supporting the concept that the tissue formed within the canal is vital and vascularized, even when it does not histologically resemble pulp tissue [33].

Controversies and Future Directions

Current Controversies

Several important controversies continue to shape the evolution of regenerative endodontics. The debate regarding the optimal disinfection protocol remains unresolved, with ongoing discussion about the relative merits of triple antibiotic paste versus calcium hydroxide as intracanal medicaments [34]. While some evidence suggests comparable clinical outcomes with both approaches, concerns about antibiotic stewardship and the potential for sensitization have increasingly favored calcium hydroxide in contemporary practice.

The question of whether the blood clot scaffold is sufficient or whether alternative scaffolds offer superior outcomes represents another area of active investigation. Clinical studies comparing platelet-rich plasma, platelet-rich fibrin, and the conventional blood clot have yielded mixed results. Some investigations have reported enhanced root development with platelet concentrates, while others have found no significant differences in radiographic outcomes [35]. The heterogeneity in study designs, outcome measures, and follow-up periods complicates definitive conclusions.

The applicability of regenerative endodontic procedures to mature teeth with closed apices remains largely experimental. The restricted apical foramen in mature teeth limits vascular ingrowth and cellular migration, presenting fundamental biological barriers to regeneration. Cell transplantation strategies, involving the ex vivo expansion of autologous dental stem cells followed by their delivery into the canal space on appropriate scaffolds, have shown promising preclinical results but face significant regulatory, logistical, and economic challenges for clinical translation [36].

Emerging Technologies

Advances in biomaterial science and molecular biology offer exciting possibilities for enhancing regenerative outcomes. Three-dimensional bioprinting of customized scaffolds with precisely controlled architecture, porosity, and growth factor distribution may overcome the limitations of the autologous blood clot [37]. Gene therapy approaches involving the transfection of stem cells with genes encoding dentin-specific proteins could direct differentiation toward true odontoblastic lineages rather than the cementoblastic pathways that currently predominate. Furthermore, the development of drug delivery systems capable of sustained, controlled release of multiple growth factors in predetermined sequences may more faithfully recapitulate the complex signaling cascades operative during natural pulp-dentin development [38].

Technological innovations have also contributed significantly to the progress of regenerative endodontics. Three-dimensional imaging modalities such as cone-beam computed tomography (CBCT) have improved diagnostic precision, enabling clinicians to better evaluate periapical pathology, root canal anatomy, and healing responses after regenerative procedures. Similarly, the incorporation of artificial intelligence (AI) into endodontic workflows has enhanced case selection, treatment planning, and predictive outcome analysis, ensuring that regenerative protocols are applied in the most effective and patient-specific manner. CBCT is more accurate than panoramic radiography and intraoral digital radiography. [39-47]

Discussion

Early stages of dental caries are reversible and can be modified or eliminated by protective factors such as fluoride exposure and salivary flow. Nanoparticles' therapeutic potential and their stimulatory effect on promoting the regeneration of cells of the dentin-pulp complex have been proven. The objectives of regenerative endodontic procedures are to regenerate pulp-like tissue, ideally, the pulp-dentin complex; regenerate damaged coronal dentin, such as following a carious exposure; and regenerate resorbed root and cervical or apical dentin. Dental caries and periodontal diseases are widely recognized as primary causes of tooth loss in adults globally. By regenerative endodontics these extractions can be prevented. [48-52]

The biological rationale is compelling, the clinical protocols have been progressively refined through accumulated experience and research evidence, and the functional outcomes, particularly in terms of periapical healing and continued root development, are well documented. However, critical evaluation of the literature reveals significant gaps that warrant attention. The vast majority of

published evidence derives from case reports, case series, and retrospective studies, with relatively few prospective controlled trials providing high-level evidence [53]. Standardization of outcome measurement remains a major challenge, as different studies employ varying methods for quantifying root development, and radiographic measurements are inherently subject to projection errors and inter-observer variability. The development and adoption of standardized, validated outcome measures would greatly facilitate meaningful comparison across studies and advancement of the field [54].

The persistent discrepancy between the clinical goal of pulp regeneration and the histological reality of predominantly periodontal-type tissue repair represents a fundamental challenge that must be addressed through deeper understanding of the biological determinants of cell fate within the regenerated canal space [55]. Identifying the specific conditions, cellular populations, scaffolds, and signaling environments that favor true pulp-dentin complex formation over cementum and bone deposition is essential for advancing regenerative endodontics beyond its current state toward genuine tissue regeneration.

The long-term durability and functional performance of regeneratively treated teeth also require further investigation. While medium-term follow-up studies spanning three to five years have generally reported favorable outcomes, data on ten-year and longer survival rates remain scarce [56,57,58]. Whether the structural reinforcement provided by regenerative tissue ingrowth and wall thickening translates to meaningful reductions in cervical root fracture rates compared to apexification represents a clinically important question that can only be answered through long-term prospective studies.

Conclusion

Regenerative endodontic procedures represent a transformative advancement in the management of immature permanent teeth with pulp necrosis, fundamentally shifting the treatment paradigm from a reparative to a biologically driven regenerative approach. The biological foundation of these procedures, built upon the tissue engineering triad of stem cells, scaffolds, and growth factors, provides a rational basis for clinical protocols that have demonstrated consistent effectiveness in achieving periapical healing and promoting continued root development. While current evidence indicates that the tissue formed within regenerated canals predominantly consists of periodontal-type tissue rather than true pulp, the functional benefits of root maturation and structural reinforcement are clinically meaningful. Future advances in scaffold design, stem cell biology, growth factor delivery, and our understanding of the molecular determinants of odontoblastic differentiation hold the

promise of achieving true pulp-dentin complex regeneration. Continued refinement of clinical protocols, standardization of outcome measures, and the conduct of well-designed prospective controlled trials will be essential for optimizing patient outcomes and establishing definitive evidence-based guidelines for regenerative endodontic practice.

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